

Figure 1

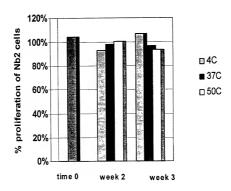


Figure 2

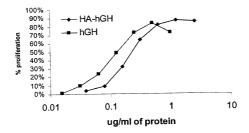


Figure 3A

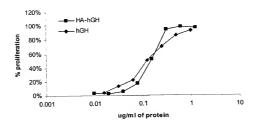


Figure 3B

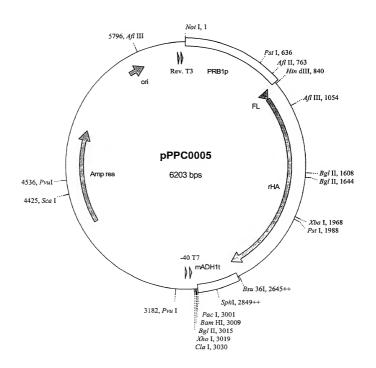


Figure 4

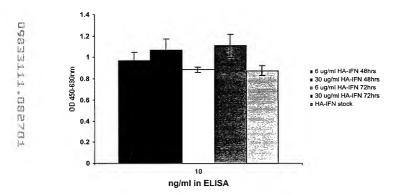


Figure 5

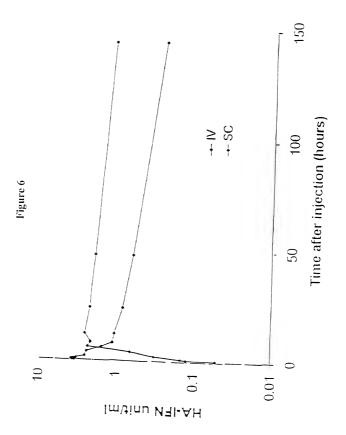
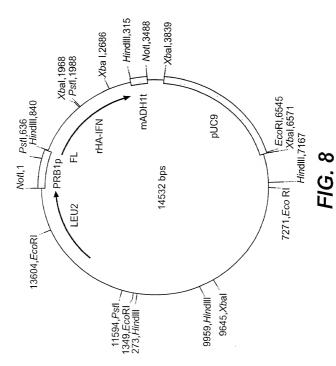


Figure 7

10x 10x --- 10x --- 117N 150 Hours after injection 50 100 10 0.001 0.1 0.01 Imtinu NAI-AH

APN: 09/833,111 7 of Craig A. Rosen et al. Atty. Docket: 6832.0014-00

7 of 20



CONSTRAIN DEPOSIT

Figure 9

1	DAHKSEVAHR HHHHH	FKDLGEENFK HHH HHH	ALVLIAFAQY ННННННННН	LQQCPFEDHV HHHHH	KLVNEVTEFA ННННННННН
	I			II	III
51	КТСV ADESAE ННННН		GDKLC TVATL HHHHH	RETYGEMADC HHHH	
101	CFLQHKDDNP HHHH			EETFLKKYLY HHHHHHHHH	
151	APELLFFAKR ННННННННН	үкаагтесс <u>о</u> нниннинн	IV AADKAACLLP HHHHH	KLDELRDEGK НННЕННННН	ASSAKQRLKC ННННННННН
201	ASLQKFGERA HHHHH HH	FKAWAVARLS ННННННННН	QRFPKAEFAE HH HHH	VSKLVTDLTK HHHHHHHHH	V VHTECC <u>HG</u> D L НННННН НН
			'I	VII	
251	LECADDRADL HHHHHHHHHH	AKYIC ENODS HHHHH		KPLLEKSHCI HHHHHHH	
301	DLPSLAADFV HHHH	ESKDVCKNYA HHHHHH			YSVVLLLRLA HHHHHHHH
		VIII			
351	KTYETTLEKC HHHHHHHHHH	C AAADPHE CY HH	AKVFDEFKPL H HHHHH	NEEPONTIKO HHHHHHHHHH	NCELFEQLGE ННННННН
					ıx
401	YKFQNALLVR ННННННННН	YTKKVPQVST HHHH H	PTLVEVSRNL HHHHHHHHHH	GKVGSKCC <u>KH</u> HHH	РЕАКРМР САЕ НИНИНИНИ
		x		ХI	
451	DYLSVVLNQL ННННННННН	CVLHEKTPVS HHHHH	DRVTKCCTES HHHHHHHHH	LVNRRPPCFSA HHHHHHHH	
501	EFNAETFTFH	ADICTLSEKE HHH HHH	RQIKKQTALV ННННММЕННН	ELVKHKPKAT HHH	KEQLKAVMDD HHHHHHHH
		XII			
551	FAAFVEKCC <u>K</u> HHHHHHHH		EGKKLVAASQ ННННННННН		
		4-Asn61	Loop VII	Glu280-His2	88
	II Thr7	6-Asp89 2-Glu100	VIII	Ala362-Glu3	368
		2-G1u100 70-Ala176	IX	Lys439-Pro4 Val462-Lys4	
		47-Glu252 66-Glu277	XI	Thr478-Pro4	186
	vi Giuz	00 0142//	XII	Lys560-Thr5	066

Figure 10

a. Randomisation of Loop IV.

ΙV

- - IV
- X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.
- b. Insertion (or replacement) of Randomised sequence into Loop IV.



IV

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.

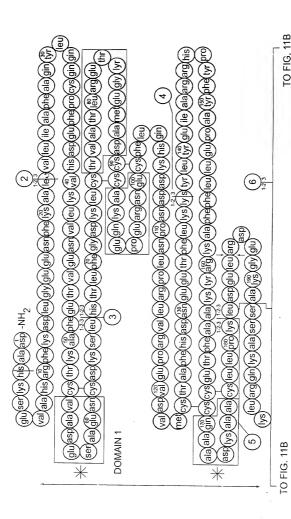
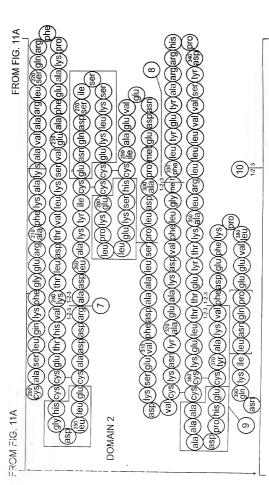


FIG. 11A



THE PROPERTY

CKETTOI

FIG. 11B

TO FIG. 11C

TO FIG. 11C

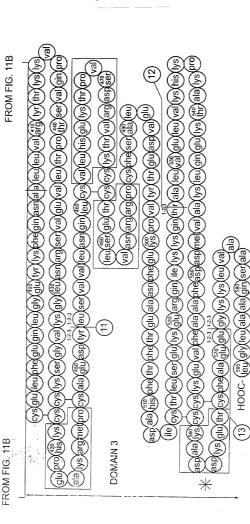
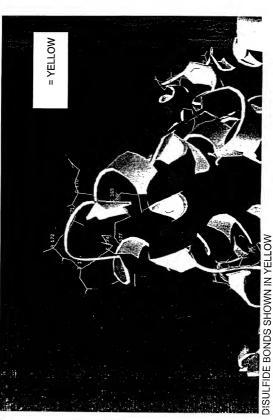


FIG. 11C



HOWN IN YELLOW **FIG. 12:** LOOP IV GLU170-A176

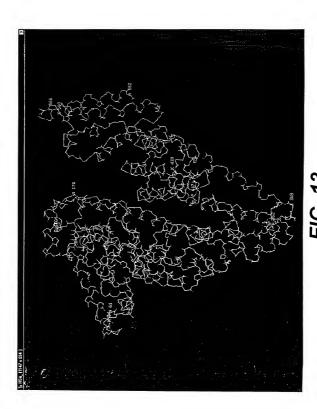


FIG. 13 TERTIARY STRUCTURE OF HA

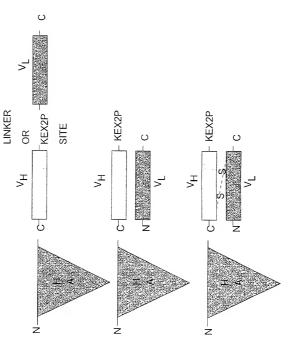


FIG. 14

60 20	120	180	240	300	360	140	480 160
AAA K	THE GIG THE AIT GCT CHE CAG TAT CAG CAG TGT CCA TUT GAR GAI CAN GTA L V L I A F A Q Y L Q Q C P F B D H V	GAA. E	CTT.	GAA E	GTT	TAT Y	AGG .
TTC	CAT H	GCT A	ACT	AAT N	GAG	TTA	AAA K
AAT N	GAT	TCA	GCA A	AGA R	CCA P	TAC Y	GCT A
GAA E	GAA.	GAG E	GTT	GAG E	AGA R	AAA K	TTT
GAA E	FTT	GAT	ACA	CCT	GTG V	AAA K	TTC
TTG GGA GAA GAA AAT L G E E N	CCA	GCT A	TGC	GAA E	TTG	$_{ m L}^{ m TTG}$	CTT
TTG L	TGT	GTT	TTA	CAA	CGA R	TTT	CTC
TTT AAA GAT 1 F K D I	CAG Q	TGT	AAA K	AAA K	TTC TTG CAA CAC AAA GAT GAC AAA CTC CCC CGA TTG GTG AGA CCA GAG GTT F L Q H K D D N P N L P R L V R P E V	ACA	GAA E
AAA K	CAG	ACA	GAC	GCA	CTC	GAG	CCG
TTT	CTT	AAA K	GGA	TGT	AAC	GAA E	GCC
200 W	TAT Y	GCA A	TTT.	TGC C	CCA P	AAT N	TAT Y
CAT H	CAG	TTT	CTT	GAC	AAC	GAC	TTT
GCT A	GCT	GAA	ACC	GCT	GAC	CAT H	TAC
GTT V	TTI	ACT T	CAT H	ATG M	GAT D	T I I	CCT
GAG E	GCC	GTA	CTT	GAA E	AAA K	GCT	CAT H
AGT	ATT	GAA E	TCA	GGT	CAC	ACT	AGA R
AAG K	TTG	AAT N	AAA K	TAT	CAA	TGC C	AGA R
CAC H	GTG	GTG	GAC	ACC	TTG	ATG	GCC
1 GAT GCA CAC AAG AGT GAG GTT GCT CAT 1 D A H K S E V A H	TTG	121 AMA TTA GTG AAT GAA GTA GGA TTT GCA AMA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180 41 K L V N E V T E F A K T C V A D E S A E GO	181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 61 N C D K S L H T L F G D K L C T V A T L	241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 81 R E T Y G E M A D C C A K Q E P E R N E	TTC	GAT GTG ATG TGC ACT GCT TTT CAT GAC AAA GAG ACA TTT TTG AAA AAA TAC TTA TAT D V M C T A F H D N E E T F L K K Y L Y	421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 141 E I A R R H P Y F Y A P E L L F F A K R
GAT D	61 GCC 21 A	AAA K	AAT N	CGT R	TGC	GAT	GAA E
	61 21	121	181	241	301	361	421 141

540 180	600	660	720	780	840 280	300	960
The arm gct cct itt aca gar ict tgc car gct gct gat arm gct gcc ctg itg cca Y K A A F T E C C Q A A D K A A C L L P	AMG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT K L D E L R D E G K A S S A K Q R L K C	AGT CTC CAA AAA TIT GAA GAA AGA GCI TIC AAA GCA TGG GCA GIG GCI CGC CTG AGC S L Q K F G E R A F K A W A V A R L S	AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720 K A E F A E V S K L V T D L T K 240	CTT 780	GCC AAG TAT ATC TGT GAA AAT CAG GAT TGG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA A K Y I C E N Q D S I S S K L K E C C E	AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT K P L L E K S H C I A E V E N D E M P A	GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGC TAT GCT AAA AAC TAT GCT D L P S L A A D F V E S K D V C K N Y A
TTG	AAA K	CTG	ACC	GTC CAC AGG GAA TGC TGC CAT GAA TGT GCT GAT GAC AGG GCG GAC	TGT	CCT	TAT Y
CTG	CTC	CGC	CTT	GCG A	TGC	ATG M	AAC N
TGC C	AGA R	GCT A	GAT D	AGG .	GAA E	GAG E	AAA K
GCC	CAG Q	GTG V	ACA	GAC	AAG K	GAT	TGC
GCT A	AAA K	GCA A	GTG	GAT	CTG	AAT N	GTT V
AAA K	GCC	W	TTA L	GCT	AAA K	GAA E	GAT D
GAT	TCT	GCA	AAG K	TGT	AGT	GTG	AAG K
GCT	TCG	A.A.A. K	TCC S	GAA E	TCC	GAA	AGT
GCT	GCT	TTC	GTT	CTT	ATC	GCC	GAA
CAA.	AAG K	GCT A	GAA E	CTG L	TCG	ATT	GTT
TGC	999	AGA R	GCA	GAT	GAT	TGC	TTT
TGT	GAA E	GAA E	TTT	GGA	CAG Q	CAC H	GAT D
GAA E	GAT D	GGA G	GAG E	CAT H	AAT N	TCC S	GCT A
ACA T	CGG R	TTT F	GCT	TGC	GAA	AAA K	GCT
TTT F	CTT	AAA K	AAA	7GC C	TGT	GAA	TTA L
GCT A	GAA E	CAA Q	000 P	GAA	ATC I	TTG	TCA
GCT A	GAT D	CTC	AGA TTT R F	ACG	TAT	CTG	CCT
AAA K	CTC	AGT	AGA R	CAC	AAG K	CCT	$_{\rm L}^{\rm TTG}$
TAT	AAG K	GCC	CAG O	GTC	GCC	AAA K	GAC
481	541	601 201	661 221	721	781	841	901 301

Figure 15B

1020 340	1080 360	1140 380	1200	1260 420	1320	1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380 441 P E A K R M P C A E D Y L S V V L N Q L 460	1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440 461 C V L H E K T P V S D R V T K C C T E S 480
GAG GCA AAG GAT GTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT. E A K D V F L G M F L Y E Y A R R H P D	THO TOT GTC GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC YSSVVLLLRLARKTYETTLEKC	CTT	TTT GAG CAG CTT GGA GAG F E Q L G E	ACT T	CAT H	TTA	TCC.
CCT	AAG K	CCT	GGA	TCA	AAA K	CAG Q	GAG E
CAT H	GAG	AAA K	CTT	GTG	TGT	AAC N	ACA
AGG R	CTA	TTT	CAG	CAA	TGT C	CTG L	TGC C
AGA R	ACT	GAA	GAG	CCC	AAA K	GTC	TGC
GCA A	ACC	GAT	TTI	GTA	AGC	GTG	AAA K
TAT Y	GAA E	TTC	CTT	AAA K	000 0	S	ACA
GAA E	TAT Y	GTG V	GAG	AAG K	GTG	CTA	GTC
TAT Y	ACA	AAA K	TGT	ACC	AAA K	TAT	AGA R
TTG L	AAG K	GCC	AAC	TAC	GGA G	GAC	GAC D
TTT	GCC.	TAT Y	CAA.	CGT R	CTA L	GAA .	AGT S
ATG	CIT	TGC	AAA K	GTT V	AAC N	GCA A	GTA
9	AGA	GAA E	ATC I	TTA L	AGA R	TGT	CCA P
CTG L	CTG L	CAT H	TTA L	CTA	TCA.	CCC	ACG T
TTC	$_{ m L}^{ m CTG}$	CCT	AAT	6CG A	GTC	ATG	AAA
GTC V	CTG	GAT	CAG Q	AAT N	GAG	AGA R	GAG E
GAT D	GTG V	GCA A	CCT	CAG	GTA V	AAA.	CAT
AAG K	GTC	GCT	GAG	TTC	CTT	GCA A	TTG L
GCA A	TCT	GCC	GAA	AAA	ACT	GAA E	GTG V
GAG	TAC	TGT	1141 GFG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT 381 V E E P Q N L I K Q N C E L	1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 401 X K K V P Q V S T	1261 CCA ACT CTT GTA GAG GTC TOA AGA RAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 421 P T L V E V S R N L G K V G S K C C K H	CCT	TGT
321	341	1081 TGT GCC GCT GCA GAN CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 361 C A A A D P H E C Y A K V F D E F K P L	1141 381	401	1261	1321	1381

Figure 15C

1500	1560 520	AGA CAA ATC AAG AAA CAA GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620 R Q I K K Q T A L V E L V K H K P K A T 540	1680	1740 580	
r ccc aaa 19 P K 50	TIT AAT GCT GAA ACA TIC ACC TIC CAT GCA GAT ATA TGC ACA CIT ICT GAG AAG GAG F N A E T F H A D I C T L S E K E	ACA T	TGC AAG 1 C K 5	CAA	
CCC	AAG K	GCA	TGC	AGT	
TTG GTG AAC AGG CGA CCA TGC TYT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT L	GAG	AAG K	TGC	GCA	
TAC Y	TCT	CCC	AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG K E Q L K A V M D D F A A F V E K	GCT	
ACA	CTT	AAG K	GAG	GTT	
GAA	ACA	CAC H	GTA V	CTT	1782 585
GAT D	TGC	AAA K	TTT	AAA K	TCT CAG
GTC V	ATA I	GTG V	GCT	AAA K	TCT
GAA E	GAT D	CTT	GCA	GGT	GCA
CTG	GCA	GAG E	TTC	GAG	CAT TTA AAA GCA
GCT.	CAT H	GTT	GAT D	GAG E	TTA
TCA	TTC	CTT	GAT	GCC	CAT
TTT	ACC	GCA	ATG	TTT	CTA
TGC	TTC	ACT	GTT.	TGC	CAT
CCA P	ACA	CAA	GCT	ACC	TAA *
CGA	GAA E	A.A.A. K	AAA K	GAG	TTA
AGG	GCT A	AAG K	CTG L	AAG K	9860
AAC	AAT N	ATC	CAA Q	GAT D	TTA
V GTG	TTT	CAA O	GAG	GAC	GCC
TTG	.501 GAG 501 E	AGA R	AAA K	GCT A	741 GCT GCC TTA GGC TTA TAA 581 A A L G L *
1441	1501	1561	541	1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 561 A D D K E T C F A E E G K K L V A A S Q	1741

Figure 15D